

### **REMARKS/ARGUMENTS**

Claims 15 and 23-28 are pending in the application and stand rejected under 35 U.S.C. §103(a) as being unpatentable over Gelfand et al. (US 6,346,379) in view of Gelfand et al. (US 6,228,628). Applicants respectfully disagree.

The Examiner states that the Gelfand '379 patent "teach a thermostable Taq polymerase comprising a F667Y mutation and a E681R mutation, wherein said thermostable DNA polymerase has reduced discrimination against incorporation of nucleotides labeled with fluorescein family dyes in comparison to the native form of said enzyme. Gelfand et al. teach that while the specific mutations at position 681 is not as critical as is the position (i.e. position 681) that is mutated."

Applicants submit that the Gelfand '379 patent does not teach an E681R mutation. Instead, it reports a Taq polymerase with the E681K (lysine) mutation. Further, while the patent stresses the importance of the 681 position what it actually says is "changes in the structure of the O<sub>a</sub>-O<sub>b</sub> helix other than E to K at position 681 are also expected to produce changes in the ability of the polymerase to discriminate against nucleotides labeled with fluorescein family dyes". Thus, they teach that some change may be expected without knowing the nature of this change except for the single mutation they studied, E681K.

In contrast, the present invention discloses a series of mutations including E681R, E681M, E681H and E681W. As demonstrated in Figures 13 and 14, and Table II, these 4 variants, and the wild-type E681 have differing behaviors in critical

applications such as DNA sequencing. This demonstrates that both the position of the amino acid change (681) and the particular amino acid substituted for E681 are important for activity.

Furthermore, Gelfand '379 patent reports discrimination against nucleotides labeled with "fluorescein family dyes" which are described as including FAM, HEX, TET, JOE, NAN and ZOE. Their examples however are limited to an undefined dye "ZOWIE" which is attached to ddCTP in an undisclosed structure. The Examples of the current application were conducted with a number of different dye-labeled nucleotides, including those tagged with rhodamine dyes ROX, R110, R6G, and TAMRA (using the nomenclature of Gelfand '379).

Gelfand et al. (US 6,228,628) does not disclose or suggest the desirability of an E681R mutation. Thus, contrary to the Examiner's assertion, none of the references disclose or suggest a Taq polymerase with a triple mutation of D18A, F667Y, and E681R.

A notice of allowance for pending claims 15 and 23-28 is earnestly requested.

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Early and favorable consideration is respectfully requested.

Respectfully submitted,

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